CLAIMS

Claims:

1. (original) A method for diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular glutathione (GSH) level.

2. (original) The method of claim 1, wherein the at least one gene involved in regulating the intracellular GSH level comprises glutamate-cysteine ligase (GCL), glutathione synthetase (GSS), glutathione peroxidase (GPX) and/or glutamate/cysteine exchange transporter (system Xc^-) gene.

3. (original) The method of claim 2, wherein GCL comprises the glutamate-cysteine ligase modulating subunit (GCLM).

4. (original) The method of claim 2, wherein GPX comprises GPX1.

5. (currently amended) The method ~~of any one~~ of claims 1 ~~to 4~~ further comprising comparing the level of expression determined for a subject with the level of expression of the corresponding at least one gene for a subject or subject population not affected by the mental disorder; wherein a difference of more than 20 percent indicates that the subject is affected or at risk of being affected by the mental disorder.

6. (currently amended) The method ~~of any one~~ of claims 1 ~~to 5~~, wherein the level of expression is determined by measuring the level of transcription of the at least one gene.

7. (currently amended) The method ~~of any one~~ of claims 1 ~~to 6~~, wherein the level of transcription is determined by at least one oligonucleotide or polynucleotide able to bind to the transcription product of the at least one gene.

8. (currently amended) The method of claim 6 ~~or 7~~, wherein the level of transcription is determined by techniques selected from the group of Northern blot analysis, reverse transcriptase PCR, real-time PCR, RNAse protection and microarray analysis.

9. (currently amended) The method ~~of any one~~ of claims 1 ~~to 5~~, wherein the level of expression is determined by measuring the level of protein expressed by the at least one gene.

10. (original) The method of claim 9, wherein the level of protein is determined by antibodies, antibody derivatives, or antibody fragments.

11. (original) The method of claim 10, wherein the level of protein is determined by Western blotting, FACS, immunohistochemistry, ELISA, ELISPOT utilizing an antibody, an antibody derivative, or an antibody fragment.

12. (original) A method for diagnosis of a mental disorder comprising determining the level of activity of at least one protein involved in regulating the intracellular GSH level.

13. (original) The method of claim 12, wherein the at least one protein comprises GCL, gamma-glutamyltransferase (GGT) and/or system Xc^-.

14. (currently amended) The method of claim 12 ~~or 13~~, wherein GCL comprises the glutamate-cysteine ligase catalytic subunit (GCLC).

15. (currently amended) The method ~~of any one~~ of claims 12 ~~to 14~~ further comprising comparing the level of activity determined for a subject with the level of activity of the corresponding at least one protein for a subject or subject population not affected by the mental disorder; wherein a difference of more than 10 percent indicates that the subject is affected or at risk of being affected by the mental disorder.

16. (currently amended) The method ~~of any one~~ of claims 12, ~~13 or 15~~, wherein the level of activity of system Xc^- is determined by measuring [^{35}S] cystine uptake.

17. (original) A method for diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular GSH level and determining the level of activity of at least one protein involved in regulating the intracellular GSH level.

18. (original) The method of claim 17, wherein at least one gene involved in regulating the intracellular GSH level comprises GCL, GCLM, GPX, GPX1, GSS

and/or system Xc^- gene and wherein the at least one protein comprises GCL, GCLC, GGT and/or system Xc^-.

19. (currently amended) The method of claim 17 ~~or 18~~, which further comprises determining the level of intracellular GSH levels.

20. (currently amended) The method ~~of any one~~ of claims 17 ~~to 19~~, wherein the level of expression of GCLM, the level of activity of GCL and the intracellular level of GSH is determined.

21. (original) The method of claim 20, wherein a decreased expression of GCLM and a negative correlation between GCL activity and GSH levels indicates that the subject is affected or at risk of being affected by the mental disorder.

22. (currently amended) The method ~~of any one~~ of claims 12 ~~to 15 or 19 to 20~~, wherein the level of activity of GCL is determined by measuring the amount of ^{14}C-γ-glutamyl-aminobutyric acid.

23. (original) A method for diagnosis of a mental disorder comprising determining the plasmatic level of at east one amino acid.

24. (original) The method of claim 23, wherein the plasmatic level of cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.is determined.

25. (currently amended) The method of claim 23 ~~or 24~~ further comprising comparing the plasmatic level of cysteine and/or homocysteine of a subject with the levels of a subject or subject population not affected by the mental disorder; wherein a difference of more than 5 percent indicates that the subject is affected or at risk of being affected by the mental disorder.

26. (original) A method for diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular GSH level and determining the plasmatic level of at least one amino acid.

27. (original) The method of claim 26, wherein at least one gene involved in regulating the intracellular GSH level comprises GCL, GCLM, GPX, GPX1, GSS and/or system Xc^- gene, and wherein the at least one amino acid comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.

28. (currently amended) The method of claim 26 ~~or 27~~, wherein the level of expression is determined for GCLM and the plasmatic levels of cystine and glutamate are determined.

29. (original) The method of claim 28, wherein a decreased expression of GCLM and an absence of correlation between cystine and glutamate levels indicates that a subject is affected or at risk of being affected by the mental disorder.

30. (original) A method for diagnosis of a mental disorder comprising determining the level of activity of at least one protein involved in regulating the intracellular GSH level and determining the plasmatic level of at least one amino acid.

31. (original) The method of claim 30, wherein the at least one protein comprises GCL, GCLC, GGT and/or system Xc^- and wherein the at least one amino acid comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.

32. (currently amended) The method of claim 30 ~~or 31~~, wherein the level of activity is determined for GGT and wherein the plasmatic level of cysteinyl-glycine is determined.

33. (original) The method of claim 32, wherein an absence of a correlation of GGT activity and the level of cysteinyl-glycine indicates that a subject is affected or at risk of being affected by the mental disorder.

34. (currently amended) The method ~~of any one~~ of claims 12, ~~13, 15 or 30 to 33~~, wherein the level of activity of GGT is determined by measuring the formation of 5-amino-2-nitrobenzoate.

35. (currently amended) The method ~~of any one~~ of claims 23 ~~to 34~~, wherein the level of amino acids is determined with an amino acid analyzer.

36. (currently amended) A method ~~of any one~~ of claims 23 ~~to 35~~, wherein the level of the at least one amino acid is determined by HPLC.

37. (original) A method for diagnosis of a mental disorder comprising determining the level of expression of at least one gene involved in regulating the intracellular glutathione (GSH) level and determining the GSH level in blood.

38. (original) The method of claim 37, wherein the level of expression is determined for GCLM.

39. (original) The method of claim 38, wherein a decreased expression of GCLM and a decrease in GSH levels indicates that a subject is affected or at risk of being affected by the mental disorder.

40. (currently amended) The method ~~of any one~~ of claims 1 ~~to 39~~, wherein the method is performed *ex vivo*.

41. (currently amended) The method ~~of any one~~ of claims 1 ~~to 40~~, wherein the mental disorder is selected from the group of schizophrenic disorders, affective disorders, psychoactive substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.

42. (original) The method of claim 41, wherein the mental disorder is schizophrenia.

43. (original) A composition for use in diagnosis of a mental disorder comprising at least one oligonucleotide or polynucleotide able to bind to a transcription product of at least one gene involved in regulating intracellular GSH level.

44. (original) The composition of claim 43, wherein the at least one oligonucleotide or polynucleotide is able to bind to a transcription product of the GCL, GSS, GPX and/or system Xc^- gene.

45. (original) The composition of claim 44, wherein GCL comprises GCLM.

46. (currently amended) The composition of claim 44, wherein ~~and~~ GPX comprises GPX1.

47. (original) The composition of claim 44, wherein the oligonucleotide or polynucleotide comprises at least one sequence selected from the group consisting of SEQ ID NO. 1 to 9.

48. (currently amended) The composition of claim 44, comprising the oligonucleotide of SEQ ID N~~o~~O 3 and/or SEQ ID 4, and optionally SEQ ID NO 2 able to bind to GSS transcripts.

49. (currently amended) The composition of claim 44 ~~or 46~~, comprising the oligonucleotide of SEQ ID No 6 and/or SEQ ID 7, and optionally SEQ ID NO 5 able to bind to GPX transcripts.

50. (original) A composition for use in diagnosis of a mental disorder comprising at least one antibody, antibody derivative or antibody fragment able to bind at least one protein involved in regulating intracellular GSH level.

51. (original) The composition of claim 50, wherein the antibody is a monoclonal antibody.

52. (original) A composition for use in diagnosis of a mental disorder comprising at least one means able to determine the activity of at least one protein involved in regulating intracellular GSH level.

53. (original) A composition of claim 51, wherein the at least one protein comprises GCL, GGT and/or system Xc^-.

54. (original) A composition for use in diagnosis of a mental disorder comprising at least one means able to determine the plasmatic level of at least one amino acid.

55. (original) A composition of claim 54, wherein the at least one amino acid comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.

56. (currently amended) A composition of claim ~~54 or 55~~, wherein the means comprise an amino acid analyzer.

57. (currently amended) The composition ~~of any one~~ of claims 43 ~~to 56~~ for use in diagnosis of schizophrenic disorders, affective disorders, psychoactive substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), or manic or psychotic depression.

58. (currently amended) The composition ~~of any one~~ of claims 43 to 57 for use in diagnosis of schizophrenia.

59.-84. (cancelled)

85. (original) A method for prevention and/or treatment of a mental disorder comprising administering an effective amount of one or more proteins to a mammal including a human, wherein the one or more protein is selected from the group consisting of

a) GCL, GSS, GPX and system Xc^- or a fragment thereof

b) a bioactive protein having a percentage of identity of at least 50% with the amino acid sequence of any one of the proteins of (a);

c) a bioactive variant of any one of the proteins of (a) or (b).

86. (original) The method of claim 85, wherein GCL comprises GCLM.

87. (original) The method of claim 85, wherein GPX comprises GPX1.

88. (currently amended) A method for prevention and/or treatment of a mental disorder comprising administering an effective amount of one or more polynucleotides to a mammal including a human, wherein the one or more polynucleotide comprises a sequence encoding a protein as defined in ~~any one of~~ claims 85 ~~to 87~~, said sequence being operatively associated with a tissue specific or a constitutive promoter.

89. (original) A method for prevention and/or treatment of a mental disorder comprising administering an effective amount of an agent that can alter the expression of at least one gene involved in regulating intracellular GSH level.

90. (original) The method of claim 89, wherein the at least one gene involved in regulating the intracellular GSH level comprises GCL, GSS, GPX and/or system Xc^- gene.

91. (original) The method of claim 90, wherein GCL comprises GCLM.

92. (original) The method of claim 90, wherein GPX comprises GPX1.

93. (original) A method for prevention and/or treatment of a mental disorder comprising administering an effective amount of an agent that can alter the activity of at least one protein involved in regulating intracellular GSH level.

94. (original) The method of claim 93, wherein the at least one protein involved in regulating the intracellular GSH level comprises GCL, GGT and/or system Xc^-.

95. (original) The method of claim 94, wherein GCL comprises GCLC.

96. (original) The method of claim, wherein GCL comprises GCLM.

97. (original) A method for prevention and/or treatment of a mental disorder which comprises administering an effective amount of an agent that can alter the plasmatic level of at least one amino acid.

98. (original) The method of claim 97, wherein the at least one amino acids comprises cystine, glutamate, cysteine, homocysteine and/or cysteinyl-glycine.

99. (currently amended) The method ~~of any one~~ of claims ~~85 to 98~~, wherein the effective amount of the protein and/or the polynucleotide and/or the agent is administered orally, sublingually, intravenously, intramuscularly, intraarticularly, intraarterially, intramedullary, intrathecally, intraventricularly, intraoccularly, intrathecally, intracereberally, intracranially, respiratorally, intratracheally, nasopharyngeally, transdermally, intradermally, subcutaneously, intraperitoneally, intranasally, enterally, or topicaly, or via rectal means, infusion or implant.

100. (currently amended) The method of ~~any one of~~ claims ~~85 to 99~~, wherein the mental disorder is selected from the group of schizophrenic disorders, affective disorders, psychoactive substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.

101. (currently amended) The method ~~of any one~~ of claims ~~85 to 102~~, wherein the mental disorder is schizophrenia.

102.-120. (cancelled)

121. (original) A method for the diagnosis of a mental disorder or a predisposition therefor in a mammal, particularly in a human being, comprising determining the presence of at least one polymorphism of at least one gene involved in regulating the intracellular glutathione (GSH) level and/or GSH-oxidative stress-related gene expression, wherein said at least one polymorphism is associated with said mental disorder or predisposition therefor.

122. (original) The method of claim 121, wherein the at least one gene involved in regulating the intracellular GSH level and/or GSH-oxidative stress-related gene expression is selected from a glutamate-cysteine ligase, modifier subunit gene (GCLM) and/or a glutathione synthetase gene (GSS).

123. (currently amended) The method of ~~any one of~~ claims 121 ~~and 122~~, wherein said polymorphism is associated with low expression levels of at least one gene involved in regulating the intracellular glutathione level and/or GSH-oxidative stress-related gene expression.

124. (currently amended) The method of ~~any one of~~ claims 121 ~~to 123~~, wherein the polymorphism is located within an intron, the 3' region and/or the 5' region of the at least one gene.

125. (currently amended) The method of ~~any one of~~ claims 121 ~~to 124~~ comprising determining a single polymorphism in a chromosomal copy of the gene, wherein said polymorphism is associated with said mental disorder or predisposition therefor.

126. (currently amended) The method of ~~any one of~~ claims 121 ~~to 125~~ comprising determining a single polymorphism in two chromosomal copies of the gene, wherein said polymorphism is associated with said mental disorder or predisposition therefor.

127. (currently amended) The method of ~~any one~~ of claims 121 ~~to 126~~ comprising determining a combination of polymorphisms in a chromosomal copy of the gene, wherein said combination of polymorphisms is associated with said mental disorder or predisposition therefor.

128. (currently amended) The method of ~~any one of~~ claims 121 ~~to 127~~ comprising determining a combination of polymorphisms in two chromosomal copies of the gene, wherein said combination of polymorphisms is associated with said mental disorder or predisposition therefor.

129. (currently amended) The method ~~fo any one~~ of claims 121 ~~to 128~~, comprising determining a combination of polymorphisms in at least one chromosomal copy of a combination of genes, wherein said combination of polymorphisms is associated with said mental disorder or predisposition therefor.

130. (currently amended) The method of ~~any one of~~ claims 121 ~~to 129~~, wherein the polymorphism of the GCLM gene is selected from the group consisting of

(a) the polymorphisms rs2235971, rs3170633, rs2064764, rs769211, rs718873, rs718875, rs2301022,

(b) polymorphisms being in linkage disequilibrium with at least one of the

polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

131. (original) The method of claim 130, wherein the polymorphism is

(a) rs2235971, rs3170633, rs769211 and/or rs2301022,

(b) in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

132. (original) The method of claim 131, wherein the polymorphism is

(a) rs3170633

(b) in linkage disequilibrium with the polymorphism of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

133. (currently amended) The method of ~~any one of~~ claims 121 ~~to 129 and 132~~, wherein the genotype of the polymorphism rs3170633 is selected from the group consisting of the nucleotides AA, AG and/or GG.

134. (original) The method of claim 133, wherein the genotype is GG.

135. (currently amended) The method of ~~any one of~~ claims 121 ~~to 129~~, wherein a combination of polymorphisms in at least one chromosomal copy of the GCLM gene is selected from the group consisting of

(a) the polymorphisms rs2235971, rs3170633, rs769211 and rs2301022,

(b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

136. (currently amended) The method of ~~any one of~~ claims 121 ~~to 129~~, wherein the polymorphism of the GSS gene is selected from the group consisting of

(a) the polymorphisms rs3746450, rs725521, rs1801310, rs2236270, rs2236271, rs2273684, rs734111, rs2025096, rs3761144,

(b) polymorphisms being in linkage disequilibrium with at least one of the

polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

137. (original) The method of claim 136, wherein the polymorphism is

(a) rs2236270, rs2273684, rs734111, rs2025096 and/or rs3761144,

(b) in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

138. (original) The method of claim 137, wherein the polymorphism is

(a) rs3761144,

(b) in linkage disequilibrium with the polymorphism of (a), and

(c) selected from combinations of polymorphisms of (a) and/or (b).

139. (currently amended) The method of ~~any one of~~ claims 121 ~~to 129~~, wherein a combination of polymorphisms in at least one chromosomal copy of the GSS gene is selected from the group consisting of

(a) the polymorphisms rs2236270, rs2273684, rs734111, rs2025096 and rs3761144,

(b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

140. (currently amended) The method of ~~any one of~~ claims 121 ~~to 129~~, wherein a combination of polymorphisms in at least one chromosomal copy of a combination of the GSS gene and the GCLM gene is selected from the group consisting of

(a) the polymorphisms rs2235971, rs3170633, rs769211, rs2301022, rs2236270, rs2273684, rs734111, rs2025096 and/or 3761144,

(b) polymorphisms being in linkage disequilibrium with at least one of the polymorphisms of (a), and

(c) combinations of polymorphisms of (a) and/or (b).

141. (currently amended) The method of ~~any one of~~ claims 121 ~~to 129~~, wherein a combination of polymorphisms in two chromosomal copies of the GCLM gene or the GSS gene is homozygous.

142. (currently amended) The method of ~~any one of~~ claims 121 ~~to 141~~, wherein the polymorphism is determined by a genotyping analysis.

143. (original) The method of claim 142, wherein the genotyping analysis comprises the use of polymorphism-specific primers.

144. (currently amended) The method of claims 142 ~~to 143~~, wherein the genotyping analysis comprises a mass-spectrometric analysis.

145. (currently amended) The method of claims 142 ~~to 143~~, wherein the genotyping analysis comprises a microarray analysis.

146. (currently amended) The method of ~~any one of~~ claims 121 ~~to 145~~, wherein the mental disorder is selected from the group of schizophrenic disorders, affective disorders, psychoaffective substance use disorders, personality disorders, delirium, dementia, epilepsy, panic disorder, obsessive compulsive disorder, intermittent explosive disorder, impulse control disorder, psychosis, attention-deficit-hyperactivity disorder (ADHD), and manic or psychotic depression.

147. (original) The method of claim 146, wherein the mental disorder is schizophrenia.

148.-188. (cancelled)